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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/491,896	01/24/2000	Matthew J. During	102194-6	9210

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/491,896	DURING, MATTHEW J.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *110-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *110-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 17 November 2004 has been entered in full. Claims 1-109 are cancelled and claims 110-118 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 110-118 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection of claims 1-3, 5-8, 22-25, 27-28, 36-40, 54, 68, 86-90, 95-97, 102-104, and under 35 U.S.C. 112, first paragraph, as set forth at pg 3-8 of the previous Office Action (14 May 2004) is *withdrawn* in view of the cancelled claims (17 November 2004). Please see section on 35 U.S.C. 112, first paragraph below with respect to new claims 110-118.

Claim Objections

2. Claim 117 is objected to because of the following informalities: Claim 117, line 1 is missing a word after the term "receptors". Please note that this issue could be overcome by amending the claim to recite, for example, the term "to" after "receptors". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. Claims 110-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for modifying the function of an N-methyl-D-aspartate receptor associated with a neurological disorder comprising administering a vaccine into the circulatory system of the subject comprising a therapeutically effective amount of a peptide antigen derived from an N-methyl-D-aspartate receptor subunit 1 (NMDAR1) wherein the peptide antigen has an antigenic region of NMDAR1 selected from the group consisting of an N-terminal extracellular domain, a preM1 region, an M4n region, an M3c region, and a region of an extracellular loop between M3 and M4 wherein the antigen elicits the production of antibodies. The claims also recite that the antibodies interact directly with the receptors to modify the function of the receptors or indirectly modify the function of a process involving the receptors.

Applicant's arguments (17 November 2004) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the previously submitted declaration (which included a manuscript) demonstrated a reduction to practice of the invention. Applicant contends that the antigen NR1 [654-800], which was shown in the manuscript to have therapeutic effects, embraced three of the claimed regions (the M3c region [641-657], the extracellular loop between M3 and M4 [681-696], and the M4n region [711-726]. Applicant argues that each of the five regions of NMDAR is enabled by the specification. Applicant submits that antigenic regions in NMDAR1 epitope were identified by epitope mapping experiments creating 94 overlapping 16mers to cover the entire 938 amino acid polypeptide of NMDAR1. Applicant states that the specification identifies six of the 16mer peptides as antigenic and which domains of NMDAR1 would raise antibodies.

Applicant's arguments (17 November 2004) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons. Additionally, the declaration of Dr. During under 37 CFR 1.132 filed 17 February 2004 has been considered by the Examiner again, but it is insufficient to overcome the rejection of claims 110-118 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph. Specifically, the declaration and manuscript are not commensurate in scope with the claims of the instant application. In the manuscript, very few animals vaccinated with NR1[21-375] peptide antigen had seizures following the induction of seizures by systemic kainite administration and direct hippocampal administration of kainic acid. Also, the manuscript teaches that animals vaccinated with NR1[654-800] peptide antigen developed seizure behaviors, but progression through the defined stages of seizure was delayed. The declaration and manuscript clearly indicate that a large region of the NR1 peptide antigen is required to have an activity (ie, NR1[654-800]). Applicant argues that NR1[654-800] peptide antigen corresponds to amino acids 641-657, 681-696, 711-726, and 791-807 (M3c domain, 2 extracellular domains between M3 and M4, and M4n domain) of the instant application (pg 57-58 of the specification). However, there are no methods or working examples in the specification or declaration indicating that an N-terminal extracellular domain, preM1 region, M4n region, M3c region, or region of an extracellular loop between M3 and M4 derived from NMDAR1 *singularly* has any activity, particularly the generation of antibodies that modify of the function of an N-methyl-D-aspartate receptor associated with all possible neurological disorders and/or ameliorate of epilepsy or other conditions associated with hippocampal dysfunction. The claims of the instant application recite administering a vaccine comprising a therapeutically effective amount of a peptide antigen derived from an N-methyl-D-

aspartate receptor subunit 1 (NMDAR1) wherein *the peptide antigen has an antigenic region of NMDAR1 selected from the group consisting* of an N-terminal extracellular domain, a preM1 region, an M4n region, an M3c region, and a region of an extracellular loop between M3 and M4 wherein the antigen elicits the production of antibodies. The claims clearly recite that the peptide antigen comprises one of five possible regions. However, is the peptide antigen also composed of other amino acids besides the sequence of an NMDAR1 antigen region? Undue experimentation would be required by the skilled artisan to generate and screen each of the NMDAR1 regions separately to determine if they have the desired activity of generating an antibody that modifies the function of an N-methyl-D-aspartate receptor associated with all possible neurological disorders and/or ameliorates of epilepsy or other conditions associated with hippocampal dysfunction. Undue experimentation would also be required by the skilled artisan to generate and screen a peptide antigen that comprises an antigenic region of NMDAR1 and another amino acid sequence. It is even noted that there is little or no guidance in the specification or declaration submitted on 17 February 2004 indicating that the peptide antigen comprising amino acids 483-498 (corresponding to the N-terminal of M1) or the peptide antigen comprising amino acids 541-566 (preM1 region) correspond to any peptide disclosed in the submitted manuscript or have any activity. The disclosure in the specification and declaration/manuscript of 17 February 2004 is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The present invention is also unpredictable and complex wherein one skilled in the art may not necessarily modify the function of an N-methyl-D-aspartate receptor associated with all possible

neurological disorders or ameliorate epilepsy or other conditions associated with hippocampal dysfunction.

Furthermore, the specification of the instant application and the declaration only disclose that peptide antigens are derived from mouse NMDAR1. A large quantity of experimentation would be required by one skilled in the art to isolate all possible NMDAR1 sequences (such as human, canine, etc. and mutations of such), as well as to identify, generate and screen each of the respective claimed NMDAR1 regions and antibodies for activity. Such experimentation is considered undue.

Due to the large quantity of experimentation necessary to isolate all possible NMDAR1 sequences, to generate and screen each NMDAR1 antigenic region separately to determine if they have a desired activity, and to modify the function of an N-methyl-D-aspartate receptor associated with all possible neurological disorders and ameliorate epilepsy or other conditions associated with hippocampal dysfunction; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of modifying the function of an N-methyl-D-aspartate receptor associated with all possible neurological disorders and ameliorating epilepsy or other conditions associated with hippocampal dysfunction, and the breadth of the claims which fail to recite limitations as to a specific NMDAR1 sequence and peptide antigen, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4. Claims 110-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for modifying the function of an N-methyl-D-aspartate receptor associated with a neurological disorder comprising administering a vaccine into the circulatory system of the subject comprising a therapeutically effective amount of a peptide antigen derived from an N-methyl-D-aspartate receptor subunit 1 (NMDAR1) wherein the peptide antigen has an antigenic region of NMDAR1 selected from the group consisting of an N-terminal extracellular domain, a preM1 region, an M4n region, an M3c region, and a region of an extracellular loop between M3 and M4 wherein the antigen elicits the production of antibodies. The claims also recite that the antibodies interact directly with the receptors to modify the function of the receptors or indirectly modify the function of a process involving the receptors.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification of the instant application and the unpublished manuscript submitted 17 February 2004 teach the generation of mouse NMDAR1 or NR1 cDNA constructs and purification of mouse NR1 recombinant proteins (see

specification pg 54, lines 15-17; manuscript pages 4-5). However, the description of one N-methyl-D-aspartate-receptor subunit 1 is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, fragments and species homologs. Similarly, the description of one N-terminal extracellular region, one preM1 region, one M4n region, one M3c region, and one extracellular domain between M3 and M4 is not adequate written description of an entire genus of functionally equivalent polypeptides which include all variants, fragments, regions, and species homologs and the antibodies that bind these variants, fragments, regions, and homologs. The specification also does not teach any specific process involving N-methyl-D-aspartate receptors that is indirectly modified by antibodies.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the NMDAR1, the peptide antigens derived from NMDAR1 and their respective antibodies, and the processes modified by antibodies encompassed by the claimed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The specific NMDAR1, peptide antigens derived from NMDAR1, and the processes modified by

antibodies are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific NMDAR1, specific peptide antigens derived from NMDAR1, and the specific processes modified by antibodies, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. Claims 117-118 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 117 is directed to antibodies interact directly with the receptors to modify the function of the receptors or indirectly modify the function of a process involving the receptors. Claim 118 recites that antibodies interact with the receptors to ameliorate epilepsy or conditions associated with hippocampal dysfunction.

The specification as originally filed does not provide adequate written description for antibodies that indirectly modify the function of a process involving the receptors. The specification as originally filed also does not provide adequate written description for conditions

associated with hippocampal dysfunction. It is not expressly asserted, nor does it flow naturally from the specification.

35 USC § 112, second paragraph

6. Claims 110-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The term "interact" in claims 110-118 (particularly claim 110, line 10; claims 117-118) is a relative term which renders the claims indefinite. The term "interact" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what activity or activities the term "interact" encompasses. (Please note that this issue could be overcome by amending the claims to recite, for example, "bind" instead of "interact".)

8. Claims 110-116 and 118 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that the function of an N-methyl-D-aspartate receptor is modified.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
04 March 2005